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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/701,789	11/05/2003	Victor J. Dzau	18989-028	7439

7590 12/01/2006

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EXAMINER	
LI, QIAN JANICE	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 12/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/701,789	DZAU ET AL.	
	Examiner	Art Unit	
	Q. Janice Li, M.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-90* is/are pending in the application.

4a) Of the above claim(s) *4-11 and 13-90* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of group I, drawn to methods of tissue regeneration using mesenchymal stem cells expressing an exogenous akt gene, and species election drawn to myocardial tissue and SDF-1 molecule, in the reply filed on 10/19/06 is acknowledged. Claims 1-3 and 12 read on the elected invention.

Claims 4-11, 13-90 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 1-3, 12 are under current examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for regenerating myocardial tissue by local administration of isolated adult mesenchymal stem cells expressing an exogenous nucleic acid encoding an akt gene, and further encoding a growth factor gene; does not reasonably provide enablement for regenerating myocardial tissue by administering, via any route, isolated adult mesenchymal

stem cells expressing an exogenous nucleic acid encoding an akt gene, and further encoding a SDF-1 gene,. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

Given the broadest reasonable interpretation, instant claims are drawn to a therapeutic method for delivering a genetically modified mesenchymal stem cell for cardiac tissue repair. The specification teaches intramyocardial injection for the recombinant cell administration. The specification is silent with respect to homing of systemic administered recombinant MSCs, e.g. whether intravenous administration would target the rMSCs to cardiac tissue in sufficient numbers to bring about a therapeutic effect.

Turning to state of the art, it appears the state of the prior art use localized delivery of therapeutic agents to cardiac tissue, for example, *Fukuda et al* (Artificial Organs 2001;25:187-93) transplanted mesenchymal stem cells into scar tissue of the heart (column 2, page 192); *Matsui et al* (Circulation 2001;104:330-5) delivering adenoviral vector expressing Akt gene via left thoracotomy into the anteroapical myocardium. Accordingly, both the specification and the state of the prior art favor localized delivery of therapeutic agent, and were silent about systemic delivery. This often reflects the state of the art concerning the feasibility of systemic delivery since mesenchymal stem cells were not known to have tropism towards myocardial tissue. Accordingly, it appears that the specification fails to provide sufficient guidance to support the full scope of the claims.

Instantly elected species of a growth factor is the SDF-1. Although the specification prophetically teach delivering such among a list of "injury-associated polypeptides" (Specification, page 9, line 7), neither the art of record nor the specification teaches how SDF-1 is associated with cardiac injury, and what kind of effect SDF-1 may assert on cardiac cells, and thus it fails to provide sufficient guidance to support the full scope of the claims.

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Matsui et al* (Circulation 2001;104:330-5), in view of *Greenberger et al* (US 5,993,801), and *Fukuda et al* (Artificial Organs 2001;25:187-93).

Matsui et al teach a method for treating cardiac injury comprising administering an adenoviral vector comprising a nucleic acid encoding a constitutively active Akt mutant via left thoracotomy into the anteroapical myocardium of cardiac ischemia model rats, and reported that Akt activation in the site of cardiac ischemia not only reduced cellular apoptosis, size of the infarction, but also dramatically improved regional cardiac functions (e.g. the abstract). *Matsui et al* do not teach administering a mesenchymal stem cell genetically modified to express the akt gene.

Greenberger et al remedy the deficiency by establishing it was well known in the art that bone marrow stromal cells (mesenchymal stem cells) could be

used as carriers for delivering an exogenous gene to a patient in need of such transgene (e.g. claims 1 and 2).

Fukuda et al remedy *Matsui et al* in view of *Greenberger et al* by establishing that it was well known in the art that mesenchymal stem cells are capable of differentiating into cardiomyocytes, and thus could be used for regenerating damaged cardiomyocytes.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Matsui et al,* with that of *Greenberger* and *Fukuda et al*, by administering mesenchymal stem cells expressing an exogenous Akt gene in place of the adenoviral vector as taught by *Matsui et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because not only MSC is a well known transgene carrier but also have the potential to directly repair/regenerating cardiomyocytes. Given that each of the cited references teaches an agent that is effective in cardiac tissue repair/regeneration, one would have had a reasonable expectation of success combining the akt nucleic acid and mesenchymal stem cells. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over *Matsui et al* (Circulation 2001;104:330-5), in view of *Greenberger et al* (US

5,993,801), and *Fukuda et al* (Artificial Organs 2001;25:187-93) as applied to claims 1-3 above, and further in view of *Palasis et al* (US 2002/0172663)

Matsui et al in view of *Greenberger* and *Fukuda et al* do not teach further delivering an exogenous nucleic acid encoding a growth factor to a heart tissue.

Palasis et al remedy the deficiency by a showing that it was well known in the art many therapeutic genes such as growth factors could be delivered locally to ischemic myocardium to promote recover from injury (e.g. claims 1, 4-7).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Matsui et al,* in view *Greenberger* and *Fukuda et al*, by administering mesenchymal stem cells expressing an exogenous Akt gene and further include a growth factor gene as taught by *Palasis et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the growth factors further promoting repair and regeneration of cardiomyocytes. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over *Matsui et al* (Circulation 2001;104:330-5), in view of *Greenberger et al* (US 5,993,801), and *Fukuda et al* (Artificial Organs 2001;25:187-93) as applied to claims 1-3 above, and further in view of *Pillarisetti et al* (Inflammation 2001;25:293).

Matsui et al in view of *Greenberger* and *Fukuda et al* do not teach further delivering an exogenous nucleic acid encoding a SDF-1 to a heart tissue.

Pillarisetti et al remedy the deficiency by a showing that it was well known in the art SDF-1 is a protein associated with cardiac infarction, and may be a therapeutic target for cardiac regeneration.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Matsui et al,* in view *Greenberger* and *Fukuda et al*, by administering mesenchymal stem cells expressing an exogenous Akt gene and further include SDF-1 gene as taught by *Pillarisetti et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because SDF-1 may further promote repair and regeneration of cardiomyocytes. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is **571-272-0730**. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The

fax numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of formal matters can be directed to the patent analyst, **William Phillips**, whose telephone number is (571) 272-0548.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

Q. JANICE LI, M.D.
PRIMARY EXAMINER

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Primary Examiner
Art Unit 1633

QJL
November 27, 2006